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09/905,592	07/13/2001	Keiya Ozawa	50026/012003	6387
21559	7590	05/11/2007		
CLARK & ELBING LLP 101 FEDERAL STREET BOSTON, MA 02110			EXAMINER SULLIVAN, DANIEL M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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Office Action Summary	Application No. 09/905,592	Applicant(s) OZAWA ET AL.	
	Examiner Daniel M. Sullivan	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 June 2006 and 27 February 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 5,6,8,12,14,15 and 17-24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 5,6,8,12,14,15 and 17-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>4/07, 2/07, 3/06, 8/06</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submissions filed on 29 June 2006 and 27 February 2007 have been entered.

Claims 5, 6, 8, 12, 14, 15 and 17-24 were considered in the Final Office Action mailed 26 January 2007. Claims 5, 8 and 14 were amended in the 29 June submission and claims 5, 8 and 14 were further amended in the 27 February submission. Claims 5, 6, 8, 12, 14, 15 and 17-24 are pending and under consideration.

Response to Amendment

Claim Rejections - 35 USC § 112

Rejection of claims 5-6, 8, 12, 14-15 and 17-24 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the disclosure does not provide adequate descriptive support for the broad scope of the claimed genus is withdrawn in view of the claim amendments.

Art Unit: 1636

Claim Rejections - 35 USC § 102

Rejection of claims 5-6, 8, 12, 15, 17 and 19-24 under 35 U.S.C. 102(e) as being anticipated by Capon et al. (US 5,838,544; reference of record) is **withdrawn** in view of the amendments and the arguments submitted with the 27 February Paper.

New Grounds

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5, 6, 8, 12, 14, 15 and 17-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The MPEP states, “[i]f new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. §112, first paragraph-written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).” (MPEP § 2163.06). The MPEP further states, “[w]henver the issue arises, the fundamental factual inquire is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of

Art Unit: 1636

the application as filed, the examiner should conclude that the claimed subject matter is not described in the application” (*Id.*, § 2163.02). The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).

In the instant case, the claims have been amended such that they are directed to a vector comprising a fusion protein that encodes a polypeptide that “(i) comprises a granulocyte-colony stimulating factor receptor deficient in amino acid residues 5 (Glu) through 195 (Leu) of wild-type murine granulocyte-colony stimulating factor receptor, or a granulocyte-colony stimulating factor receptor deficient in amino acid residues 5 (Glu) through 195 (Leu) and amino acid residues 725 through 756 of wild-type murine granulocyte-colony stimulating factor receptor, and (ii) imparts proliferation activity to a cell, upon dimerization of said first polypeptide.”

As written, the polypeptide of the claims embraces a (i.e., any) granulocyte-colony stimulating factor (G-CSF) receptor, wherein the receptor is deficient in a region from a glutamate at residue 5 of the murine receptor through a leucine at position 195 of the wild-type murine receptor. In addition, the polypeptide might be deficient in amino acids 725-756 of the wild-type murine G-CSF receptor.

In support of these new limitations, Applicant cites a passage at page 9, lines 12-14, which describes the construction of a species of fusion protein comprising a modified G-CSF receptor. The cited Example reads in full (emphasis added):

In order to produce a chimeric protein comprising the entire G-CSF receptor and the ligand (estrogen)-binding domain of the estrogen receptor (hereafter

Art Unit: 1636

designated simply as "GCRER"), the fusion gene having cDNAs that encode the respective proteins (FIG. 1(A)) was constructed. Next, a mutant of the fusion gene, "GCRER," which is deficient in the 5th residue, Glu, through the 195th residue, Leu, of the G-CSF receptor extracellular domain (hereafter designated simply as "GCRA(5-195)/ER") was constructed, in order to produce a chimeric protein that lacks reactivity against G-CSF (FIG. 1(B)). Further, a mutant was constructed by deleting a portion containing the differentiation-inducing domain (725-756) of the G-CSF receptor from the mutant (hereafter designated simply as "GCRA(5-195, 725-756)/ER") (FIG. 1(C)).

Applicant further submits a Declaration by Dr. Yasuji Ueda wherein Dr. Ueda states in paragraph 2:

G-CSF receptors are a class of proteins that were extraordinarily well characterized at the time the application was filed. The structural features, including the Immunoglobulin-like domain, the cytokine receptor homologous domain, the three fibronectin type III domains, and the intracellular domain, defining this class of receptors were also known. For instance, Fukunaga et al. (Cell 61:341-350, 1990; copy enclosed as Exhibit A) describes the murine G-CSF receptor sequence and notes that the sequence is highly homologous to that of the human G-CSF receptor. Larsen et al. (J. Exp. Med. 172:1559-1570, 1990; copy enclosed as Exhibit B) describes the human G-CSF receptor sequence. In addition, Fukunaga et al. (EMBO J.: 10:2855-2865, 1991; copy enclosed as Exhibit C) describes functional domains of human and mouse G-CSF receptors. In view of the knowledge in the art at the time the application was filed, a skilled artisan would readily recognize a G-CSF receptor sequence.

While the arguments and evidence of record support a claim wherein the second polypeptide comprises a modified murine G-CSF receptor comprising a deletion of amino acids 5 (Glu) through 195 (Leu) of the wild-type murine granulocyte-colony stimulating factor receptor extracellular domain, or a modified murine granulocyte-colony stimulating factor receptor comprising a deletion of amino acid residues 5 (Glu) through 195 (Leu) of the wild-type murine granulocyte-colony stimulating factor receptor extracellular domain and amino acid residues 725 through 756 of wild-type murine granulocyte-colony stimulating factor receptor

Art Unit: 1636

differentiation-inducing domain, the record as a whole does not evidence that the invention presently claimed was disclosed in the application as filed.

First, Figure 5 of Fukunaga et al. (of record in the instant application and cited by Dr. Ueda in the Declaration) shows that the fifth amino acid of the murine G-CSF receptor is not a glutamate¹. Therefore, the skilled artisan would not recognize a G-CSF receptor sequence comprising a glutamate at position 5 of the polypeptide. However, Fukunaga et al. does teach that the first 25 amino acids of the nascent polypeptide are cleaved to form the mature polypeptide and teaches a transmembrane domain beginning at about amino acid 602. (See especially the Figure 5 and the caption thereto). Therefore, the skilled artisan would recognize the amino acid sequence beginning at the cysteine identified as amino acid 1 in Figure 5 of Fukunaga et al. through amino acid 601 as the “extracellular domain” of the polypeptide, and that the murine sequence does comprise a glutamate at position 5 of this extracellular domain. Thus, the skilled artisan would recognize, given the description in the specification and the knowledge of the murine G-CSF receptor sequence, the disclosure of a modified murine receptor comprising the specified deletions in the extracellular and differentiation-inducing domains.

In contrast, the human receptor sequence does not comprise a glutamate at position 5 of the nascent polypeptide and additionally does not comprise a glutamate at position five of the mature polypeptide. In the sequence of Larsen et al. (of record in the instant application and cited by Dr. Ueda in the Declaration), the fifth amino acid of the mature polypeptide is an isoleucine (see Figure 1 and the caption thereto) and in the alignment of the murine and human sequences provided in Figure 4A of Larsen et al. the relevant glutamate of the murine sequence is aligned

¹ Amino acid number 5 is a glycine.

Art Unit: 1636

with a serine. Therefore, the skilled artisan would conclude that the discussion of the deletion mutants presented in the specification as filed can only be referring to the murine sequence that was known in the art at the time of filing because it is the only sequence of record that comprises the features discussed in the application. Therefore, a claim that recites any polypeptide other than the murine polypeptide comprising the deletions disclosed in the application as filed constitutes impermissible new matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Capon et al. U.S. Patent No. 5,837,544 (previously made of record) in view of Benjamin Lewin, Genes V, Oxford University Press, Oxford, New York, Tokyo, 1994, p. 634.

As described in previous Office Actions, the '544 patent teaches a chimeric constructs encoding a ligand-binding domain and a proliferation signaling domain (PSD), as well as vectors and cells containing said constructs. (e.g. Abstract; columns 22-25, Example 1; describing construction of various fusion proteins). The chimeric constructs also encode transmembrane domains (i.e., exogenous genes). (e.g., col. Figure 1). In addition, the chimeric construct can comprise an inducer-responsive clustering domain (ICD), i.e. hormone receptor domain, which upon binding the inducer or ligand will dimerize or cluster. (e.g. col. 3, ll. 33-39; See also, Fig. 1). Furthermore, the ICD domains can be eukaryotic steroid receptor molecules, including estrogen, progesterone, androgen, for example. (e.g., col. 14, last ¶). In addition, the PSD portion of the chimeric construct can be the transducing domains (i.e. proliferation domains) of the cytokine receptors, including IL-2 for example. (e.g. col. 16, last ¶ bridging to col. 17, ll. 1-19). Further, the PSD can be G-CSF. (e.g. col. 9, l. 54).

Thus, Capon et al. teaches a vector comprising a gene encoding a fusion protein that comprises a ligand-binding domain of a steroid hormone receptor that, upon ligand binding, dimerizes, and a second polypeptide comprising a G-CSF receptor. Capon et al. does not explicitly teach that the vector should also comprise a "desired exogenous gene". However, Capon et al. does teach that the constructs described therein can be "introduced into vectors for cloning in an appropriate host, e.g., *E. Coli*." (Column 19, first full paragraph.)

Lewin teaches, "Many plasmids carry genes that specify resistance to antibiotics. This feature is useful in designing cloning systems. A common procedure is to use a plasmid that has genes specifying resistance to two antibiotics. One of the genes is used to identify bacteria that carry the plasmid. The other is used to distinguish chimeric plasmid s from parental vectors."

Art Unit: 1636

(Page 634, final full paragraph.) Thus, Lewin teaches that “desired exogenous genes” such as selectable marker genes are commonly found in vectors used for cloning nucleic acids such as the vectors contemplated by Capon et al.

It would have been obvious to one of ordinary skill in the art to include a desired exogenous gene, such as the marker genes described by Lewin et al. in the vector construct of Capon et al. One would be motivated to include the marker genes in view of the teaching of Lewin that such genes are useful in designing cloning systems and one would have a reasonable expectation of success in view of the fact that selectable markers had been routinely used in cloning systems for many years prior to the filing date of the instant application.

Thus, in view of the foregoing, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claim is properly rejected under 35 USC §103(a) as obvious over the prior art.


Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Joseph Woitach, Ph.D. can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1636

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


Daniel M. Sullivan, Ph.D.
Primary Examiner
Art Unit 1636